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Helicobacter pylori eradication treatment and the risk of gastric adenocarcinoma in a Western population

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ABSTRACT (word count: 245)

Objective: Gastric colonization with *Helicobacter pylori* is a strong risk factor for non-cardia gastric adenocarcinoma. The aim of this study was to assess whether the risk of gastric adenocarcinoma and non-cardia gastric adenocarcinoma decreases after eradication treatment for *Helicobacter pylori* in a Western population.

Design: This was a nationwide, population-based cohort study in Sweden in 2005-2012. Data from the Swedish Prescribed Drug Registry provided information on *Helicobacter pylori* eradication treatment whereas information concerning newly developed gastric adenocarcinoma was retrieved from the Swedish Cancer Registry. The risk of gastric adenocarcinoma and non-cardia gastric adenocarcinoma in individuals who had received *Helicobacter pylori* eradication treatment was compared with the background population of the corresponding age, sex and calendar year distribution, yielding standardized incidence ratios (SIRs) with 95% confidence intervals (95% CIs).

Results: During the follow-up of 95,176 individuals who had received eradication treatment (351,018 person-years at risk), 75 (0.1%) developed gastric adenocarcinoma and 69 (0.1%) developed non-cardia gastric adenocarcinoma. The risk of gastric adenocarcinoma decreased over time after eradication treatment to levels below that of the corresponding background population. The SIRs were 8.65 (95% CI 6.37-11.46) 1-3 years, 2.02 (95% CI 1.25-3.09) 3-5 years, and 0.31 (95% CI 0.11-0.67) 5-7.5 years after eradication treatment. When restricted to non-cardia adenocarcinoma, the corresponding SIRs were 10.74 (95% CI 7.77-14.46), 2.67 (95% CI 1.63-4.13), and 0.43 (95% CI 0.16-0.93).

Conclusion: Eradication treatment for *Helicobacter pylori* seems to counteract the development of gastric adenocarcinoma and non-cardia gastric adenocarcinoma in this Western population.

Keywords: *Helicobacter pylori*; gastric neoplasm; gastric cancer; antibiotic treatment; Sweden.

SIGNIFICANCE OF THIS STUDY

What is already known about this subject?

- The strongest risk factor for non-cardia gastric adenocarcinoma is gastric colonisation with *Helicobacter pylori*.
- Only a small percentage (3%) of those colonised with *Helicobacter pylori* develop non-cardia gastric adenocarcinoma.
- Eradication of *Helicobacter pylori* is associated with a reduced risk of gastric cancer in Asian populations.

What are the new findings?

- This study assessed the role of *Helicobacter pylori* eradication treatment in the prevention of gastric adenocarcinoma in a large population-based study, using data from high-quality nationwide Swedish registers.
- The risk of gastric adenocarcinoma (non-cardia adenocarcinoma in particular) sharply decreased from 5 years onwards after eradication treatment for *Helicobacter pylori*.

How might it impact on clinical practice in the foreseeable future?

- The findings of this study may contribute to a better understanding of the risks and benefits of eradication therapy in regions with a low prevalence of gastric cancer.

INTRODUCTION

Globally, gastric cancer (95% adenocarcinoma) is the fifth most common cancer (incidence rate 16.1 per 100,000 individuals) and the second most common cause of cancer death (death rate 13.8 per 100,000 individuals).[1] The highest incidence is found in Asian populations, and the lowest in Western populations.[1] In Sweden (a Western population), the incidence rates are 10.4 and 6.4 per 100,000 individuals in men and women, respectively.[2] Colonization with the bacterium *Helicobacter pylori (H. pylori)* is associated with an increased risk of non-cardia gastric adenocarcinoma, whereas the risk of cardia gastric adenocarcinoma is not increased.[3] Worldwide, around half of the population is colonized, with higher rates in Asia and Central and South America, and lower rates in Western populations.[4] The *H. pylori* prevalence in Sweden is around 15%, which is relatively low.[5] Of those colonized, it is estimated that the lifetime risk of developing gastric adenocarcinoma is around 3%.[6]

H. pylori eradication, mainly used for the prevention of recurrent peptic ulcer after an earlier ulcer episode, has been found to prevent gastric cancer in meta-analyses, showing a 50% risk reduction.[7,8] However, these meta-analyses almost exclusively included studies from Asian populations and the individual studies had small sample sizes. Thus, there is a need to estimate the role of *H. pylori* eradication treatment in the prevention of gastric cancer in large-scale studies from Western populations with specific analyses of the risk of non-cardia adenocarcinoma. Therefore, this study aimed to assess the risk of gastric adenocarcinoma and of non-cardia gastric adenocarcinoma after eradication treatment for *H. pylori* in a nationwide Swedish cohort study.

MATERIALS AND METHODS

Study design

This was a population-based, nationwide cohort study in Sweden, based on an a priori established study protocol. The exposure was eradication treatment for *H. pylori* and the outcomes were gastric adenocarcinoma and non-cardia gastric adenocarcinoma. Eligible for inclusion were all individuals residing in Sweden aged 18 years and older who received eradication treatment for *H. pylori* during July 1st, 2005 to December 31st, 2012. The cohort has been described in more detail elsewhere.[9] The study was approved by the Regional Ethical Review Board in Stockholm (2014/1291-31/4).

Exposure

Individuals were considered exposed if they received at least one prescription and dispensing of a recommended eradication regimen for *H. pylori*. Eradication treatment for *H. pylori* in Sweden usually consists of a combination of a proton pump inhibitor together with the antibiotics amoxicillin and clarithromycin for 7 days.[9] The following prescriptions are available in Sweden for recommended eradication treatment of *H. pylori* (specified by the Anatomical Therapeutic Chemical code):

- A specific *H. pylori* eradication package that includes the proton pump inhibitor esomeprazole and the antibiotics amoxicillin and clarithromycin (A02BD06);
- Separate prescriptions of a proton pump inhibitor (A02BC) together with 2 of the following antibiotics: amoxicillin (J01CA04) and clarithromycin (J01FA09) or metronidazole (J01XD01).

For the separate prescriptions, no other antibiotics were to be prescribed at the same time in order to be considered a recommended regimen. Additionally, the antibiotics had to be prescribed on the exact same date, whereas the proton pump inhibitor was allowed to be

prescribed within a window of 60 days before or 5 days after the antibiotics prescription. This window was chosen to include individuals already using a proton pump inhibitor before the eradication treatment, and to take temporary non-availability in the pharmacy into account. Recommended eradication regimens accounted for 95.4% of all eradication treatments prescribed in Sweden during the study period.[9] The remaining 4.6% of the treatments included combinations of antibiotics that are not standard for *H. pylori* eradication and were therefore not included in this study.

Outcomes

The outcomes were first and primary gastric adenocarcinoma and non-cardia gastric adenocarcinoma diagnosed in the Swedish Cancer Registry during follow-up of the cohort after *H. pylori* eradication treatment, excluding tumours occurring within 1 year of the eradication treatment. Gastric cancer was defined by any of the following ICD7 codes: 151, 151.0, 151.1, 151.8 and 151.9, whereas the code for cardia cancer (151.1) was excluded when analysing non-cardia cancer. Adenocarcinoma histology was determined using the code 096 from the C24 World Health Organization classification of histology. Other histological types of gastric malignancies are not associated with *H. pylori* (or have a different level of association, e.g. mucosa-associated lymphoid tissue lymphoma), and therefore were excluded.[10]

Confounders

Adjustments were made for age (categorized into the age groups 18-59, 60-69, or ≥70 years), sex (men or women), and calendar period (2005-2006, 2007-2009, or 2010-2012) by standardizing these variables. Place of residence (urban or rural), which is correlated with socioeconomic and lifestyle factors,[11] was analysed for influence on the outcome.

Data sources

The Swedish Prescribed Drug Registry provided information on *H. pylori* eradication treatment. This register started on July 1, 2005 and contains information on all prescribed and dispensed medications for the whole Swedish population. Patient identifying data are missing in only <0.3% of all recorded prescriptions.[12] Variables used were the age, sex, postal code (to assess place of residence),[11] unique personal identity number of each individual, and the substance, dates, amount and dosage of the dispensed drugs.

The Swedish Cancer Registry provided information on gastric and non-cardia gastric adenocarcinoma. This register has a completeness of 98% for recording of non-cardia adenocarcinoma.[13] Data on the histological type and location of the cancer, and date and age at cancer diagnosis was used, and all these variables are 100% completely recorded in the register.

The Swedish Causes of Death Registry was used to assess dates of death. This information is virtually 100% complete and was used for censoring of follow-up time.[14]

Statistical analysis

Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated as the ratio of the observed number of gastric and non-cardia gastric adenocarcinoma cases in the *H. pylori* eradication cohort, compared to the expected number of such cases in the Swedish population of the same sex, age group, and calendar period with categorization as presented above (subtitle "Confounders"). Clayton's algorithm was used to calculate the follow-up time in person-years for each stratum, starting from the date of the first dispensed prescription of *H. pylori* eradication treatment.[15] This index date was chosen as time zero to emulate a randomized clinical trial.[16] Additionally, a "per-protocol" analysis was performed

which started from the last dispense date of eradication treatment. Individuals were followed up until the occurrence of any cancer, death, or the end of the study period, whichever occurred first. Subgroup analyses were performed for the time after eradication treatment (grouped into 1-3, 3-5, and 5-7.5 years), and the number of received eradication treatments (1, 2, and ≥ 2). More than 1 eradication treatment indicated that *H. pylori* remained present after the previous treatment attempt, thus prolonging the colonization time in the individual. Poisson regression was used to analyse potential confounding by place of residence (urban or rural), and to assess any influence of the length of follow-up, presented as incidence rate ratios (IRRs) and 95% CIs. The statistical software STATA (Stata Corp v. 13.0, College Station, TX) was used for all analyses.

RESULTS

Participants

The study included 95,176 individuals receiving *H. pylori* eradication treatment during the study period (Table 1). There were more men (53.7%) than women (46.3%) and the majority was younger than 60 years (60.1%). Most individuals resided in urban areas (74.6%). The mean length of follow-up was 3.7 years (maximum 7.5 years). During 351,018 person-years at risk, 75 (0.1%) individuals developed gastric adenocarcinoma and 69 (0.1%) developed non-cardia gastric adenocarcinoma.

Table 1: Descriptive characteristics of the cohort of individuals receiving at least one eradication regimen for *Helicobacter pylori* in Sweden during 2005-2012.

Characteristic	Participants Number (%)
Total	95,176 (100.0)
Sex	
Men	44,028 (46.3)
Women	51,148 (53.7)
Age (years)	
18-59	57,214 (60.1)
60-69	17,808 (18.7)
≥ 70	20,154 (21.2)
Calendar period	
2005-2006	21,218 (22.3)
2007-2009	38,573 (40.5)
2010-2012	35,385 (37.2)
Place of residence	
Rural	23,686 (24.9)
Urban	71,032 (74.6)
Missing	458 (0.5)
Type of cancer	
All gastric adenocarcinoma	75 (0.08)
Non-cardia gastric adenocarcinoma	69 (0.07)
Cardia adenocarcinoma	6 (0.01)
Follow-up (years)	
Total	351,018
Mean	3.7

Helicobacter pylori eradication treatment and risk of all gastric adenocarcinoma

The SIRs decreased with longer time after eradication treatment. The SIRs were 8.65 (95% CI 6.37-11.46) 1-3 years, 2.02 (95% CI 1.25-3.09) 3-5 years, and 0.31 (95% CI 0.11-0.67) 5-7.5 years after eradication treatment (Table 2). Poisson regression with 1-3 years after eradication treatment as the reference group, showed IRRs of 0.05 (95% CI 0.03-0.09) 3-5 years and 0.00 (95% CI 0.00-0.01) 5-7.5 years after eradication treatment. Analysis from the date of last eradication treatment ("per protocol") showed a similar trend, with decreased risks from ≥5 years after eradication treatment (data not shown). The risk of gastric adenocarcinoma increased with a higher number of eradication treatments, from SIR 1.88 (95% CI 1.44-2.41) in individuals with 1 eradication treatment to SIR 7.44 (95% CI 2.72-16.19) in those with more than 2 eradication treatments (Table 2). Poisson regression showed no difference in gastric adenocarcinoma risk between individuals residing in rural or urban areas (IRR 0.98, 95% CI 0.59-1.61; p = 0.93).

Table 2: Risk of gastric and non-cardia gastric adenocarcinoma in individuals receiving *Helicobacter pylori* eradication treatment in Sweden from 2005-2012 compared to the Swedish standard population, expressed as standardized incidence ratio (SIR) with 95% confidence interval (CI)

	Gastric adenocarcinoma		Non-cardia gastric adenocarcinoma	
	Number	*SIR (95% CI)*	*Number*	*SIR (95% CI)*
Total	75	2.08 (1.63-2.60)	69	2.64 (2.06-3.35)
Follow-up time, years				
1-3	48	8.65 (6.37-11.46)	43	10.74 (7.77-14.46)
3-5	21	2.02 (1.25-3.09)	20	2.67 (1.63-4.13)
5-7.5	6	0.31 (0.11-0.67)	6	0.43 (0.16-0.93)
Number of eradications				
1	61	1.88 (1.44-2.41)	56	2.38 (1.80-3.10)
2	8	2.84 (1.22-5.59)	7	3.45 (1.38-7.11)
>2	6	7.44 (2.72-16.19)	6	10.47 (3.82-22.78)

Women had a higher risk of gastric adenocarcinoma 1-3 years after eradication treatment (SIR 11.69, 95% CI 7.49-17.40), compared to men (SIR 6.86, 95% CI 4.39-10.20), but the SIRs were similar after 3 years of follow-up (Table 3). Younger age was associated with a higher risk of gastric adenocarcinoma, especially 1-3 years after eradication treatment (Table 3).

Table 3: Risk of gastric adenocarcinoma in individuals receiving *Helicobacter pylori* eradication treatment in Sweden from 2005-2012 compared to the Swedish standard population stratified by sex, age and calendar period, expressed as standardized incidence ratio (SIR) with 95% confidence interval (CI)

	Time after eradication					
	1-3 years		3-5 years		5-7.5 years	
	Number	*SIR (95% CI)*	*Number*	*SIR (95% CI)*	Number	SIR (95% CI)
Total	48	8.65 (6.37-11.46)	21	2.02 (1.25-3.09)	6	0.31 (0.11-0.67)
Sex						
Men	24	6.86 (4.39-10.20)	13	2.02 (1.08-3.46)	4	0.34 (0.09-0.87)
Women	24	11.69 (7.49-17.40)	8	2.03 (0.87-4.00)	2	0.26 (0.03-0.93)
Age, years						
18-59	14	25.71 (14.04-43.14)	4	3.57 (0.96-9.15)	0	NA
60-69	8	5.95 (2.56-11.71)	4	1.52 (0.41-3.88)	1	0.18 (0.00-1.02)
≥70	26	7.10 (4.64-10.40)	13	1.96 (1.05-3.36)	5	0.43 (0.14-1.00)

Helicobacter pylori eradication treatment and risk of non-cardia gastric adenocarcinoma

The SIRs of non-cardia gastric adenocarcinoma decreased with longer duration after eradication treatment, with SIRs of 10.74 (95% CI 7.77-14.46) 1-3 years, 2.67 (95% CI 1.63-4.13) 3-5 years, and 0.43 (95% CI 0.16-0.93) 5-7.5 years after eradication treatment (Table 2). Multiple eradication treatments increased the risk of non-cardia gastric adenocarcinoma, from SIR 2.38 (95% CI 1.80-3.10) in those with 1 eradication treatment to SIR 10.47 (95% CI 3.82-22.78) in those with more than 2 eradication treatments (Table 2).

Eradication treatment for *H. pylori* did not influence the overall risk of cardia adenocarcinoma (SIR 0.60, 95% CI 0.22-1.30), but there were too few cases (6 cases) to provide robust results regarding time latencies after eradication treatment of *H. pylori* and the risk of this tumour.

DISCUSSION

This study showed that the risk of gastric adenocarcinoma and non-cardia gastric adenocarcinoma declined over time after eradication treatment for *H. pylori* and was lower than that of the background population from 5 years after eradication treatment.

Methodological strengths of this study include the population-based design, large sample size, and the high-quality data in the registers used. Additionally, studies on this topic have rarely been performed on a Western population, thus this study assesses a gap of knowledge. Also, non-cardia gastric adenocarcinoma was analysed separately, the gastric cancer type known to be associated with *H. pylori,* which was not always the case in earlier studies. The study also has limitations. The registers do not contain information on some potential confounders, e.g. socioeconomic status. However, there was no effect of place of residence, which is correlated with socioeconomic status and lifestyle factors like smoking, diet, and physical activity. Another limitation was the relatively short duration of follow-up. However, the maximum length of follow-up was still 7.5 years and the study had sufficient statistical power for robust analyses, including in the longest follow-up category. The fact that parts of the background population were colonized with *H. pylori* would dilute the risk estimates, but not explain them, and this dilution should be limited because the population prevalence of *H. pylori* infection in Sweden is relatively low (15%).[5] Additionally, the participants who received *H. pylori* eradication treatment were included in the background population, but because the study participants represented only a small proportion of the population (1.3%), this is unlikely to have had major influence on the results. If anything, it would again have diluted the associations, and not explain them. Another limitation is the lack of information about eradication treatments received before July 2005, making it unclear whether the first eradication date in the study was in fact the first eradication attempt. However, there is low

antibiotic resistance in Sweden,[17] and only 9% of all cohort members received more than 1 eradication treatment during the study period, making this a minor issue. There was no confirmation of eradication success, meaning that *H. pylori* might still have been present after treatment. This should explain the higher risk among individuals receiving multiple eradication treatments compared to those with only one (more likely to be successful) eradication treatment.

The clearly decreasing risk after eradication treatment over time is reassuring and in line with the results of meta-analyses from predominantly Asian populations.[7,8] Compared to previous cohort studies on this topic, where the largest studies included 3,781 individuals receiving *H. pylori* eradication treatment,[18] this study is considerably larger. A randomized clinical trial included 1,130 individuals receiving eradication treatment with a maximum follow-up of 14.7 years, where an odds ratio of 0.61 (95% CI 0.38-0.96) was found for gastric cancer, compared to a placebo group (n=1,128).[19] However, that study did not analyse adenocarcinomas or non-cardia cancers separately. Of all previous randomized clinical trials or cohort studies, only one was conducted in a Western population, i.e. in Finland with low prevalence of *H. pylori* and low risk of gastric cancer.[20] The results of the present study are in line with the Finnish study, showing a strong decrease starting from the sixth year after eradication therapy. However, in this study adenocarcinoma was not assessed separately.

In conclusion, this population-based Swedish cohort study showed a sharp decrease in risk of gastric adenocarcinoma and non-cardia gastric adenocarcinoma after eradication treatment for *H. pylori*. The risk was below the level of the background population 5 years after the eradication treatment. Thus, eradication treatment for *H. pylori* seems to prevent the development of gastric and non-cardia gastric adenocarcinoma also in Western populations.

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COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

Design of the study: all authors; Data collection and preparation for analyses: NB and ED; Data analysis: ED with support from NB; Data interpretation: all authors; Writing of first draft: ED, revised and approved by all authors.

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